REMARKS

Claims 22-33 and 49-92 are pending in the subject application. Claims 22, 26-28, 30, 31, 33, 53, 64, 90 and 92 have been amended. The amendments to claims 22, 26-28, 30, 31, 33, 53, 64, 90 and 92 are supported by the specification as filed, and no new matter is presented. Favorable reconsideration in light of the remarks which follow is respectfully requested.

1. 35 U.S.C §112 Rejections

Claims 22-33 have been rejected under 35 U.S.C.§112, second paragraph, as being indefinite. In particular, the Office asserts:

> It is unclear as to what applicant intends to convey by 'if there is a solubilizing point' in claim 22 (step e); if there is a solvent, then won't there be a solubilizing point?

Applicants have amended claim 22 herein and the terminology pointed to by the Office has been deleted. Thus, this rejection is moot. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office further asserts that:

> It is also unclear what the expression 'the reference particles are water molecules' in step f is intended to convey. One molecule of any compound cannot be seen by the naked eye or even an electron microscope. How can these be considered as particles?

Applicants have amended claim 22 herein and the terminology pointed to by the Office has been deleted. Thus, this rejection is moot. Reconsideration and withdrawal of the rejection is respectfully requested.

> Claim 92 which is dependent from 22 recites 'wherein the transfersomes are produced by a method selected from ---'. Claim 22, however, deals with a method of production of transfersomes. Is the step recited in claim 92 an additional step?

Applicants respectfully submit that claim 22 recites a "method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal." As set out, the method comprises selecting a first amphiphilic lipid component, a second amphiphilic component and at least one active ingredient. The method further comprises producing a vesicle suspension by means of

applying energy to the mixture of the first and second amphiphilic components including at least one active ingredient, and adjusting the content of the amphiphilic components as specified.

Claim 92 further specifies that the vesicles of claim 22 are produced, in particular, by a method selected from the group consisting of filtration, treatment with ultrasound, stirring and shaking. In other words, claim 22 merely states that the vesicle suspension is produced by means of applying energy to the mixture. Claim 92 further specifies that the vesicles are produced by filtration, treatment with ultrasound, stirring or shaking. Thus, claim 92 merely specifies that means of applying energy to the mixture can be filtration, treatment with ultrasound, stirring or shaking. Thus, Applicants respectfully submit that the claim is clear as written. Reconsideration and withdrawal of the rejection is respectfully requested.

2. Double Patenting

U.S. Patent No. 6,165,500

Claims 53-91 have been rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 6,165,500 (US'500). The Office asserts that:

> Instant claims are drawn to treatment of a mammal by administering the same transfersomes to the skin or mucous membrane of the mammal. Since the transfersomes have to be transported through the skin as claimed in patented claims, instant claims encompass the patented claims. Instant claim 53 is generic with respect to the amount of the lipid and the lipid surfactant ratios in patented claims.

Applicants respectfully traverse.

As set forth in the MPEP, a double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. §103 " except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. §103 obviousness determination. *In*

re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); MPEP §804.

Applicants claim, in claim 53, a method of treatment of a mammal in need thereof, the method comprising administering to the skin or mucous membrane of the mammal a preparation for the transport of at least one active agent through the skin or mucous membrane of the mammal. Applicants' preparation comprises vesicles suspended in a pharmaceutically acceptable medium for application onto the skin or mucous membrane of a mammal. The vesicles comprise liquid droplets encompassed within a sheath, and the sheath comprises (1) a first amphiphilic lipid component, a second amphiphilic component and at least one active agent, or (2) a first amphiphilic lipid component, a second amphiphilic component comprising an amphiphilic active agent and, optionally, one or more further active agents. In particular, the first and second amphiphilic components differ in their solubility in said pharmaceutically acceptable medium by a factor of at least 10. Further, the first and second amphiphilic components are selected such that said, independently of the concentrations of the first and second amphiphilic components and the active ingredient, no solubilization of the vesicles in the suspension occurs. Further, the vesicles are capable of undergoing sufficient deformation to pass through said skin or mucous membrane without being solubilized. Further, the active agent(s) are contained in the liquid droplets, in the sheath, or in both the liquid droplets and sheath, or the active agent(s) are identical to the more soluble amphiphilic component

Similarly, Applicants claim, in claim 22, a method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal. Applicants' method comprises selecting a first amphiphilic lipid component, selecting a second amphiphilic component and selecting at least one active ingredient. In particular, the first and second amphiphilic components are selected so that the solubility of the second amphiphilic component in a pharmaceutically acceptable suspending medium is at least ten times greater than the solubility of the first amphiphilic lipid component in the medium. The first and second amphiphilic components and active ingredients are further selected such that, independently of the concentrations of the first and second amphiphilic components

and the active ingredient, no solubilization of the vesicles in the suspension occurs. Applicants' method further comprises producing a vesicle suspension by means of applying energy to the mixture of the first and second amphiphilic components including at least one active ingredient. The vesicles are produced so as to comprise liquid droplets of the suspension medium encompassed within a sheath comprising the first and second amphiphilic components. Applicants' method further comprises adjusting the content of the amphiphilic components such that the vesicles are capable of undergoing sufficient deformation to pass through said skin or mucous membrane without being solubilized. As further specified, the active ingredient is contained in the liquid droplets or in the sheath, or in both the liquid droplets and the sheath.

Thus, Applicants have discovered a new method for producing a preparation and a new method for the treatment of a mammal comprising administering to the skin or mucous membrane of the mammal a preparation for the transport of at least one active agent through the skin or mucous membrane of the mammal. Applicants' preparation provides important benefits not addressed to date. In particular, Applicants preparation comprises vesicles suspended in a pharmaceutically acceptable medium. The vesicles comprise liquid droplets encompassed within a sheath. The sheath comprises a combination of a first and second amphiphilic component and at least one active agent. In one embodiment, the at least one active agent is the second amphiphilic component. Applicants have found that it is possible to provide preparations with vesicles that will not solubilize in the suspension regardless of how much of the first and second amphiphilic component and active ingredient(s) are added. These vesicles are also capable of undergoing sufficient deformation to pass through said skin or mucous membrane without being solubilized.

Thus, the components may be added in almost any concentration without solubilization of the vesicles. Applicants found that this is possible because for certain substance compositions, there is a saturation limit of one of the components in the membrane-like sheath of the vesicles and, as soon as this limit is reached, the addition of further amounts of this component will not lead to further incorporation of such molecules into the membrane. Rather, such addition will simply cause an

increase in the free-floating of such molecules in the suspension medium. The vesicles remain stable and do not get solubilized. This is an important aspect of the present invention and has not been taught or described to date.

Prior references do not teach or suggest such preparations. Rather, all of the prior references, including US'500 describe preparations wherein a solubilizing point is present. For example, it is set forth in US'500 that:

> The preparation contains a concentration of edge active substances which amounts to up to 99 mol-% of the agent concentration which is required for the induction of droplet solubilization. (Abstract)

According to US'500, certain conditions must be determined and met in order to provide a useful preparation:

> At first, the conditions are determined under which the carrier vesicles are solubilized by the edge active substances. At this critical point the `vesicles` are maximally deformable owing to the fact that they are permanently formed and deformed. At the same time, however, they are also unstable and incapable of holding and transferring water soluble substances.
>
> Next, the carrier composition or concentration is adapted by reducing the edge activity in the system to an extent which ensures the vesicle stability as well vesicle deformability to be sufficiently high; this also ensures the permeation capacity of such carriers to be satisfactory. The term stability in this application implies, on the one hand, a mechanical tendency of the carrier components to "stay together"; on the other hand, that the carrier composition during the transport, and in particular during the permeation process, does not change at all or not much. The position of the corresponding optimum which one is looking for hereby depends on many boundary conditions. The type of agent molecules also plays an important role in this. The smaller and the more hydrophilic the agent to be transported, the further the carrier system must be spaced from the solubilization point; the desired shelf life of carriers is also important: upon approaching the solubilization point, the tendency of transfersomes to form larger particles may increase and the carrier's storage capacity simultaneously decrease. (Col . 50, lines 32-59)

Thus, with US'500, if too much of a particular component is present in the preparation, the droplets will solubilize, thus rendering the preparation ineffective. The present invention, on the other hand, provides the unique advantage in that solubilization will not occur regardless of the concentration of the components. Thus,

for example, with prior methods, if a mere fraction of one component is added in excess and solubilization occurs, the entire batch of the pharmaceutical preparation is useless and must be discarded. With the present invention, this is not a risk because no solubilization will occur. Further, with prior preparations and methods of production, one must first determine the solubilization point prior to determining the concentration of components that can be successfully added without causing solubilization. With the present invention, because there is no solubilization, one need not carry out this additional step.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

A set forth above, US'500 does not teach or suggest all the claim limitations of Applicants' claims 22 or 53. Further, there is no suggestion or motivation to modify US'500 so as to meet Applicants' claims. Thus, claims 2 2and 53 are patentable over US'500. Claims 23-33, 49-52 and 54-92 depend from claims 22 and 53 and, likewise, are patentable over US'500. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Application No. 10/357,618

Claims 22-33 have been provisionally rejected as being unpatentable over claims 69-87 and 101-103 of copending Application No. 10/357,618. The Office asserts that:

> [I]nstant claims 22-33 and 92 and the claims 69-79 are drawn to a method of preparation of same transfersomes; instant claim language does not exclude the presence of the third substance in the method of preparation and the generic claim 69 in said copending application

encompasses instant molar amounts. Instant claims 49-91 are drawn to a method of treatment using the transfersomes and thus encompases 'a method for generating a therapeutic effect on a warm blood creature applying transfersomes; as stated above, instant claim language does not exclude the presence of the third substance in the composition used in the method of generating a therapeutic effect in the claims of said copending application.

Applicants respectfully traverse.

As set forth above, Applicants have discovered a new method for producing a preparation for the transport of at least one active agent through the skin or mucous membrane of the mammal. Applicants' preparation provides important benefits not addressed to date. In particular, Applicants preparation comprises vesicles suspended in a pharmaceutically acceptable medium. The vesicles comprise liquid droplets encompassed within a sheath. The sheath comprises a combination of a first and second amphiphilic component and at least one active agent. In one embodiment, the at least one active agent is the second amphiphilic component. Applicants have found that it is possible to provide preparations with vesicles that will not solubilize in the suspension regardless of how much of the first and second amphiphilic component and active ingredient(s) are added. These vesicles are also capable of undergoing sufficient deformation to pass through said skin or mucous membrane without being solubilized.

Application No. 10/357,618 does not describe or suggest such a preparation for the same reasons as set forth above regarding US'500. Thus, claim 22 is patentable over Application No. 10/357,618. Claims 23-33, 49-52 and 91 depend from claim 22 and, likewise, are patentable over Application No. 10/357,618. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

3. 35 U.S.C. §012 Rejections

Claims 22-33 and 49-92 have been rejected under 35 U.S.C. §102(b) as being anticipated by EP 0 475 160 of record (English equivalent US 6,165,500). Applicants respectfully traverse.

As set forth above, Applicants have discovered a new method for producing a preparation for the transport of at least one active agent through the skin or mucous membrane of the mammal. Applicants' preparation provides important benefits not addressed to date. In particular, Applicants preparation comprises vesicles suspended in a pharmaceutically acceptable medium. The vesicles comprise liquid droplets encompassed within a sheath. The sheath comprises a combination of a first and second amphiphilic component and at least one active agent. In one embodiment, the at least one active agent is the second amphiphilic component. Applicants have found that it is possible to provide preparations with vesicles that will not solubilize in the suspension regardless of how much of the first and second amphiphilic component and active ingredient(s) are added. These vesicles are also capable of undergoing sufficient deformation to pass through said skin or mucous membrane without being solubilized.

Prior references do not teach or suggest such preparations. Rather, all of the prior references, including US'500 describe preparations wherein a solubilizing point is present.

As provided in MPEP-2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Or stated another way, "The identical invention must be shown in as complete detail as is contained in the ... claims. *Richardson v Suziki Motor Co.*, 868 F.2d 1226, 9 USPQ 2d. 1913, 1920 (Fed. Cir. 1989). Although identify of terminology is not required, the elements must be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

It is clear from the foregoing that the present claims are not anticipated by US'500. In particular, Applicants teach a method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal and methods for use of such preparations. According to Applicants, the preparation comprises first and second amphiphilic components selected such that, independently of the concentrations of the first and second amphiphilic components

and the active ingredient, no solubilization of the vesicles in the suspension will occur. US'500, on the other hand, specifically describes that the preparations indeed have solubilization points and that one must determine what the solubilization point is and adjust the components and concentrations accordingly in order to produce a useful preparation.

Thus, with US'500, if too much of a particular component is present in the preparation, the droplets will solubilize, thus rendering the preparation ineffective. The present invention, on the other hand, provides the unique advantage in that solubilization will not occur regardless of the concentration of the components. Thus, for example, with prior methods, if a mere fraction of one component is added in excess and solubilization occurs, the entire batch of the pharmaceutical preparation is useless and must be discarded. With the present invention, this is not a risk because no solubilization will occur. Further, with prior preparations and methods of production, one must first determine the solubilization point prior to determining the concentration of components that can be successfully added without causing solubilization. With the present invention, because there is no solubilization, one need not carry out this additional step and the risk of solubilization does not exist.

Clearly, each and every element as set forth in claim 22 is <u>not</u> described, either expressly or inherently, in the US'500 reference. Thus, claim 22 is not anticipated by the US'500 reference. Claims 23-33, 49-52 and 92 depend from claim 22 and, likewise, are not anticipated by US'500. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

4. <u>35 U.S.C. §103 Rejections</u>

Claims 22-33 and 49-92 have been rejected under 35 U.S.C. §103(a) as being unpatentable over EP 0 475 160 (English equivalent US 6,165,500). Applicants respectfully traverse.

As set forth above, Applicants have discovered a new method for producing a preparation for the transport of at least one active agent through the skin or mucous membrane of the mammal and methods for use of such preparations. Applicants'

preparation provides important benefits not addressed to date. In particular, Applicants preparation comprises vesicles suspended in a pharmaceutically acceptable medium. The vesicles comprise liquid droplets encompassed within a sheath. The sheath comprises a combination of a first and second amphiphilic component and at least one active agent. In one embodiment, the at least one active agent is the second amphiphilic component. Applicants have found that it is possible to provide preparations with vesicles that will not solubilize in the suspension regardless of how much of the first and second amphiphilic component and active ingredient(s) are added. These vesicles are also capable of undergoing sufficient deformation to pass through said skin or mucous membrane without being solubilized.

Prior references do not teach or suggest such preparations. Rather, all of the prior references, including US'500 describe preparations wherein a solubilizing point is present.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

A set forth above, US'500 does not teach or suggest all the claim limitations of Applicants' claims 22 or 53. Further, there is no suggestion or motivation to modify US'500 so as to meet Applicants' claims. Thus, claims 2 2and 53 are patentable over US'500. Claims 23-33, 49-52 and 54-92 depend from claims 22 and 53 and, likewise, are patentable over US'500. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Reconsideration and allowance of claims 22-33 and 49-92 is respectfully requested in view of the foregoing discussion. This case is believed to be in condition for immediate allowance. Applicant respectfully requests early consideration and allowance of the subject application.

Applicants believe that no extension of time is required since this response is being filed before the expiration of the specified time period. Applicants, however, conditionally petition for an extension of time to provide for the possibility that such a petition has been inadvertently overlooked and is required. As provided below charge Deposit Account No. **04-1105** for any required fee.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

Respectfully submitted,

Date: 12/21/04

Lisa Swiszcz Hazzard (Reg. No. 44,368)
EDWARDS & ANGELL, LLP
P.O. Box 9169
Boston, MA 02209
Tel. No. (617) 517-5512